Women and Ischemia Syndrome Evaluation (WISE)
Diagnosis and Pathophysiology of Ischemic Heart Disease
Workshop

October 2-4, 2002

General Session

Topic and Author
Overview of the Field: Status & Challenges. Dr. Noel Bairey Merz
2. Where we stand in 2002. Overview/rationale for inclusion of topic.

Women's Ischemia Syndrome Evaluation (WISE)

There are three critical paradoxes with regard to the subject of women and ischemic heart disease. First, women demonstrate more symptoms of ischemic heart disease, yet have a lower prevalence of obstructive coronary disease, compared to men. Second, among patients with obstructive coronary disease, women have more "atypical" symptoms and/or noninvasive test findings suggesting silent ischemia compared to men. Thirdly, once women present with obstructive coronary disease they appear to have more adverse outcomes, including death, compared to men. This third paradox suggests that investigation relative to improving the symptom recognition and diagnosis of ischemic heart disease in women could lead to improved outcomes, and lives saved.

The objective of the Women's Ischemia Syndrome Evaluation (WISE) (Bairey Merz) is to enhance the understanding of the pathophysiology of suspected myocardial ischemia and to develop accurate diagnostic strategies for ischemic heart disease in women. The WISE study has three primary aims:

1) To improve diagnostic testing for ischemic heart disease in women, including symptom evaluation tools, risk assessment algorithms, and non-invasive imaging techniques;
2) To study pathophysiologic mechanisms and prognosis in women with symptoms and evidence of myocardial ischemia in the absence of obstructive coronary disease
3) To evaluate the influence of cyclical hormones, menopausal status and reproductive hormone levels on symptoms and diagnostic testing results.

This cross-sectional study has successfully met all three of these primary aims. A total of 936 women undergoing coronary angiography for suspected myocardial Ischemia have been enrolled, underwent diagnostic testing, and are currently being followed. Most of the WISE women have multiple cardiac risk factor conditions, commonly hypertension, obesity, and diabetes. Most are postmenopausal (75%) and 46% currently use hormone replacement therapy. Compared to female cohorts from HERS, Framingham, PEPI, the WISE has the greatest representation of minority women (19%)(Bairey Merz). To date, the WISE has published numerous manuscripts and many more abstracts have been presented at major scientific sessions. All of these WISE publications are notable in that they provide new data that begins to fill the void of information needed to advance our understanding with regard to ischemic heart disease in women.

Some of the major WISE findings to date are briefly summarized below:

1. Female Angina differs from Male Angina

The clinical diagnosis of myocardial ischemia in women has been a challenge. The traditional anginal symptom assessment was developed and tested primarily in men. The WISE developed a female angina assessment for identification of significant coronary disease. Ongoing evaluation of the data reveal differences (male oriented vs. female oriented) in symptom quality. Compared to traditional typical angina characteristics, the WISE female angina variables that correlate with significant coronary disease include: 1) arm or shoulder pain, 2) no neck pain, and/or 3) no palpitations. Predictive accuracy using a logistic regression model estimating $\geq$50% coronary disease stenosis in at least one epicardial coronary artery reveals odds ratios of 1.8- to 2.3- fold higher for the WISE sex-specific model compared to the traditional angina model after controlling for other qualitative pain descriptors. A pattern of chest symptom assessment specifically designed in the WISE has the potential to offer improved diagnostic accuracy for obstructive coronary disease for women. While the qualities of 1) substernal pain, 2) exertional pain, 3) relief with rest or nitro accurately identifies obstructive coronary disease in men, the preliminary WISE results suggest that traditional predictive models developed in predominantly male populations may not be optimally accurate in women (Johnson submitted).

The WISE results confirm the expectation that chest pain *per se* is not an adequate predictor of significant coronary artery disease in women and highlight the need for a more sensitive diagnostic algorithm. These analyses are ongoing and will assess the relationship of presenting symptoms with long-term clinical outcomes.

2. Microvascular Dysfunction Is Prevalent in Women and May Explain the Paradox of Symptoms and Signs of Ischemia without Obstructive Coronary Disease

The WISE data show that nearly half of these contemporary women with chest discomfort and no significant coronary obstruction have abnormal flow reserve (Reis). A similar percentage has coronary artery endothelial dysfunction, while approximately 25% exhibit evidence for ischemia by abnormal myocardial high energy phosphate metabolism. Analyses using PET have confirmed limited coronary flow reserve and endothelial dysfunction that appears to be more global, rather than localized to specific arteries (Reis). These findings suggest that there may be multiple mechanisms of macro-and microvascular dysfunction in these women, reflected by coronary flow and metabolic abnormalities that may explain signs and symptoms of ischemic heart disease in the absence of obstructive coronary disease. In addition to offering an explanation to the symptom paradox observed in women, the myocardial phosphate findings (Buchthal) should provide a pathophysiological basis for new treatment development. Furthermore, these findings were detected noninvasively by cardiac magnetic resonance spectroscopy and have potential for a new testing modality.

Furthermore, WISE analyses show that endothelial dysfunction, measured by flow-mediated brachial artery reactivity and resting diameter, is a correlate of angiographic coronary disease severity (Holubkov). Therefore, endothelial dysfunction measured by brachial artery diameter and function may be another useful noninvasive test to predict future cardiovascular events in women.

3. ***Premature Ischemic Heart Disease in Women Appears to be Related to Estrogen-Deficiency***

The WISE has shown, examining younger, premenopausal women, that when more careful measurements of reproductive hormone blood levels were determined in women not taking exogenous oral contraceptives or hormone replacement therapy, the women with hypothalamic hypoestrogenemia (estradiol level <50 pg/ml, FSH and LH both <10 mIU/ml) had a significantly greater prevalence of significant coronary disease (75% vs 31%, $p<0.02$, respectively) compared to women with higher estrogen levels (Bairey Merz in press). These data indicate that these premenopausal women with obstructive coronary disease are estrogen-deficient, due to hypothalamic dysfunction. These data are in accord with results from primate studies

showing environmental stress-induced hypothalamic hypoestrogenemia with anovulatory cycling and experimental atherosclerosis. This new finding offers insight into both the third paradox of more adverse outcomes in women, and provides a platform to develop new, gender-specific hormonal treatments for Ischemic heart disease.

Preliminary data from a WISE ancillary study also suggest that plant estrogens (phytoestrogens) play a key role in coronary artery dysfunction and lipoproteins. Higher levels of the phytoestrogen genistein were associated with significantly greater limitations in coronary flow reserve (p=0.03)(Johnson abstract). These are the first human data to suggest potentially adverse effect of phytoestrogens. The phytoestrogen, daidzen, had no association with these coronary physiolgoic measures. Daidzen was associated with significantly lower total cholesterol, triglycerides and LDL-C, and significantly greater HDL-C (p<.001)(Bairey Merz in press). Both of these associations were independent of age and estrogen status. These findings could have important implications for the increasingly frequent use of phytoestrogens by women.

4. Yo-Yo Dieting is Associated with Low HDL-cholesterol in Women

There are data suggesting that weight cycling (yo-yo dieting) is associated with increased cardiac mortality. The WISE described, for the first time, a potential mechanism responsible for this association, by publishing an association between reported weight cycling and lower HDL-cholesterol (Olson).

5. Exercise Electrocardiography.

The diagnostic accuracy of exercise electrocardiography reported in the WISE shows 33% sensitivity and 66% specificity for detection of obstructive coronary disease ($\geq$50% stenosis in at least one epicardial coronary artery); a results lower than those obtained in males (Holubkov). A sizable proportion of this group were unable to exercise adequately to achieve a diagnostic heart rate response, due to low baseline functional status and comorbidity, despite use of a gender-specific graded exercise ramp protocol, underscoring the need for improved noninvasive testing and alternate diagnostic algorithms for women.

6. Stress echocardiography.

Using dobutamine stress echocardiography (DSE), the overall sensitivity and specificity was 40% and 80.6% respectively in the WISE population (Lewis). Notably, a significant proportion (15%) of the women had indeterminate tests due to inability to achieve an adequate peak heart rate before developing intolerable symptoms or cardiovascular side effects. Of these, a third had severe coronary artery stenosis ($\geq$ 50% stenosis), as compared to 27% of the overall study population. Sensitivity improved to 50% when excluding women with indeterminate DSE and to 81.8% for two- or three-vessel stenosis. Thus, reliably detecting multivessel stenosis, DSE is usually negative in women with single-vessel disease. The results demonstrate the need for improved diagnostic accuracy in women with single-vessel disease.

7. Stress Radionuclide Perfusion and MR perfusion imaging.

Preliminary studies using magnetic resonance and nuclear perfusion imaging to detect coronary disease in women show promise. The WISE protocol comparatively studied cardiac MRI perfusion with intravenous gadoteridol as well as rest and intravenous dipyridamole nuclear SPECT imaging. MRI improved accuracy (sensitivity and specificity of 88% and 77%) for identification of obstructive coronary disease ($\geq$50% stenosis in at least one epicardial coronary artery) compared to Tc-99m sestamibi at rest and at peak exercise (75% sensitivity and 83% specificity)(Doyle abstract). Although these results are more promising than those of exercise stress ECG and stress echocardiography, they underscore the need for the development of a diagnostic algorithm for obstructive coronary disease in women.

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